REMARKS

This Amendment is filed in response to the non-final Office Action dated January 22, 2008, and is respectfully submitted to be fully responsive to the rejections raised therein. Accordingly, favorable reconsideration on the merits and allowance are respectfully requested.

In the present Amendment, claims 1, 3, 6, 11 and 12 have been amended to improve their form.

Claim 4 and 13 have been amended by inserting the full name for the abbreviations "CRH-R1" and "CRH-R2", and by inserting the recitation ---wherein the one or more synthetic CRH-R1 antagonists and/or CRH-R2 agonists is directly modifying a response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis--- into the claims.

Claim 15 has been newly added and is directed to excipients recited in claim 6 as filed on November 2, 2007.

No new matter has been added. Support for the claim amendments can be found in the specification on page 4, lines 22-25 and 28, for example. Entry of the Amendment is respectfully submitted to be proper. Upon entry of the Amendment, claims 1-15 will be all the claims pending in the application.

As an initial matter, Applicants request consideration and acknowledgement of Applicants' foreign priority claim under 35 U.S.C. § 119(a)-(d) or (f), and confirmation of receipt of Applicants' foreign priority document, Greece 20020100513.

The present invention relates to therapeutic modalities in the treatment of acute or chronic inflammatory diseases using synthetic corticotrophin-releasing hormone receptor 1

("CRH-R1") antagonist and/or a synthetic corticotrophin-releasing hormone receptor 2 ("CRH-R2") agonists as a therapeutic regimen.

I. Election/Restriction

Applicants thank the Examiner for rejoining Group IV and further acknowledging the election of Group III[3] and Group IV[4], claims 4-10, 13 and 14 directed to pharmaceutical compositions and kits, for examination.

II. Response to Claim Objections

Independent claims 4 and 13 are objected to for informalities. Specifically, the Examiner indicates that claims 4 and 13 should be amended to include the full name for the abbreviations CRH-R1 and CRH-R2.

Applicants submit that the claims have been amended accordingly. Withdrawal of the objection is respectfully requested.

III. Rejections Under 35 U.S.C. § 112, First Paragraph Enablement/Written Description

Claims 4-10, 13 and 14 are rejected under 35 U.S.C. § 112, first paragraph as assertedly lacking enablement and written description.

Applicants traverse and request reconsideration and withdrawal of the rejection in view of the claim amendments and in further view of the following remarks.

Independent claim 4, as amended, recites a pharmaceutical composition comprising one or more synthetic corticotrophin-releasing hormone receptor 1 ("CRH-R1") antagonists and /or

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[3] Group III, claims 4-10, 13 and 14 (in part), drawn to pharmaceutical compositions and kits comprising CRH-R1 antagonists.

[4] Group IV, claims 4-10, 13 and 14 (in part), drawn to pharmaceutical compositions and kits comprising CRH-R2 agonists.

corticotrophin-releasing hormone receptor 2 ("CRH-R2") agonists, wherein the one or more synthetic CRH-R1 antagonists and/or CRH-R2 agonists is directly modifying the response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis.

Independent claim 13, as amended, recites a kit for the treatment of an inflammatory disease or condition comprising one or more corticotrophin-releasing hormone receptor 1 (CRH-R1) antagonists and/or corticotrophin-releasing hormone receptor 2 (CRH-R2) agonists comprised in one of more individual pharmaceutical compositions, wherein the one or more synthetic CRH-R1 antagonists and/or CRH-R2 agonists is directly modifying the response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis.

Applicants submit that the scope of claims 4-10 and 13-14 are enabled by the present specification, and that one skilled in the art would be able to make and use the entire scope of the claimed invention without undue experimentation. According to the present specification, the invention is directed to the use of synthetic CRH-R1 receptor antagonists and/or a synthetic CRH-R2 receptor agonists in the treatment of acute or chronic inflammatory disease. The present specification teaches that *in vivo*, *in vitro* and human experiment models have been used to demonstrate the regulatory role of the CRH system on monocyte/macrophages.[5] It has been demonstrated in both *in vitro* and *in vivo* that CRH-R1 agonist augments inflammatory response, that CRH-R1 antagonists ameliorates inflammatory response, and that CRH-R2 agonists ameliorates inflammatory response.

Further, Applicants submit that the specification describes the claimed invention in sufficient detail so that one skilled in the art can reasonably conclude that the inventor had

[5] See, Specification on page 5, lines 1-30 and page 6, lines 1-8.

possession of the claimed invention. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics and the method of making the claimed invention. The present claims have adequate support in the specification. Furthermore, the claims are drawn to pharmaceutical compositions comprising "synthetic" CRH-R1 antagonists and/or CRH-R2 agonist, which requires the compound to be manufactured. Therefore, the scope of the claims recite that which a skilled artisian could envision. Additionally, as mentioned above, the specification provides adequate disclosure of invention, and how to make and use the invention.

Specifically, the specification discloses three examples of compounds usable in the method of the invention having the claimed features, namely synthetic antalarmin, CRH and endogenous urocortin. "Synthetic CRH-R1 antagonist" is defined in the present specification as a synthetic compound that inhibits CRH-R1 function and when added to a CRH-R1 assay blocks the effects of CRH peptides and the effects of synthetic CRH-R1 agonists, resulting in a smaller signal when the CRH-R1 receptor is stimulated with a agonist ligand therefore, such as CRH, compared with same assay but without said compound. A "synthetic CRH-R2 agonist" is defined as a synthetic compound that activates CRH-R2 and in a CRH-R2 assay gives rise to a signal as a result of the CRH-R2 receptor activation, such as CRH, compared with same assay but without said compound. (See Specification on page 6, lines 27-30 and on page 7, lines 1-5). Thus, a synthetic CRH-R1 antagonist falling within the scope of the claim is a compound which inhibits CRH-R1 function. Such inhibition is caused by monocyte/macrophage cell activation, proliferation, differentiation or apoptosis as recited in the present amended claims.

The process of measuring inhibition is very well known within the art. For example, one of the most commonly used techniques is enzyme linked immuno-sorbent assay (ELISA). Thus, inhibition can be measured using well-known assays where the effects of CRH peptides and of synthetic CRH-R1 agonists, for example, are blocked by a compound of the invention, in this instance a CRH-R1 antagonist. Examples of such assays are described in the specification on page 7 lines 7-22, for example. These assays (e.g., ELISA, RIA and *in vivo* studies) are further exemplified in the experimental section of the specification, e.g., on page 16, and 22-24.

It is known to one skilled in the art that all known endogenous as well as synthetic agonists and antagonists of CRH receptors are classified according to their resemblance to the prototypes of CRH and urocortin (endogenous agonists of CRH receptors) and to antalarmin (synthetic antagonist of CRH receptors). Thus, regarding the disclosure of the present invention, one skilled in the art would consider the terms "CRH", "urocortin" and "antalarmin" as representative models of molecules having the function of modulating immune response and inflammation via the same CRH-receptor system. Applicants, therefore, submit that one skilled in the art would appreciate that the examples of tests given in the present specification is applicable to other CRH-R1 antagonists and CRH-R2 agonists.

Additionally, the CRH receptors are well known. Therefore, one skilled in the art would know what the effect of the function of the antagonist/agonist on the receptor would be. Further to this point, the specification further describes how to determine whether a given compound is an antagonist/agonist on page 6, line 27 to page 7 line 5. Disclosure of how to determine whether a compound possesses the desired function is disclosed along with well-known assays for performing such experiments. Additionally, the present specification also discloses what the

function of the receptor is. It is thus submitted that the compounds of the invention are sufficiently disclosed.

The assertion that there are limitless structural possibilities to the compounds of the invention is irrelevant to the determination to whether one skilled in the art can make and/or use the invention. In the present case, the structural variation of possible compounds is limited by the resemblance to the model structures and in particular to a testable narrowly defined activity, namely whether the compound is able to activate/inhibit the receptors. The amount of experimentation, if necessary, would not be undue.

In view of the above, it is respectfully submitted that the claims are enabled and comply with the written description requirement.

IV. Response to Rejection Under 35 U.S.C. § 102(b) Based on Webster

Claims 4-10 and 13-14 are rejected under 35 U.S.C. § 102(b) as being anticipated by Webster et al., Endocrinol. 1996; 137: 5747-5750 ("Webster").

Applicants traverse and request reconsideration and withdrawal of the rejection in view of the claim amendments and in further view of the following remarks.

Webster describes antalarmin as an ameliorate of the severity of inflammation. However, Webseter does not describe or examine the cellular and signaling mechanisms of this beneficial effect (e.g., effect was specific or non-specific due to a generalized suppression of the immune system, which would have compromised severely its potential use) of the specific CRH antagonist that was used, or if the effect was simply a deleterious effect on multiple types of immune cells lacking any safe therapeutic potential. Thus, Webster does not disclose that the antagonist is directly modifying the response of monocyte/macrophage cell activation,

proliferation, differentiation or apoptosis. Accordingly, the present amended claims are not anticipated by Webster.

V. Response to Rejection Under 35 U.S.C. § 102(b) Based on Habib

Claims 4-7, 9, 10 and 13-14 are rejected under 35 U.S.C. § 102(b) as being anticipated by Habib et al., PNAS, 2000; 97:6079-6084 ("Habib").

Applicants traverse and request reconsideration and withdrawal of the rejection in view of the claim amendments and in further view of the following remarks.

Habib teaches that CRH plays a broad role in the physiological responses to psychological stress in primates and that a CRH type 1 receptor antagonist may be therapeutic in treating psychiatric, reproductive and cardiovascular disorders associated with CRH system hyperactivity. Anticipation requires the express or implicit description in a disclosure of each element and limitation recited in the rejected claim. Habib does not teach a pharmaceutical composition or kit for treating an inflammatory disease using CRH antagonists/agonists, wherein the CRH antagonists/agonists is directly modifying the response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis. Thus, claims 4 and 13 do not read on the subject matter described in Habib. Withdrawal of the rejection is respectfully requested.

VI. Rejection Under 35 U.S.C. §102(b) Based on Wei

Claims 4-8 and 13 are rejected under 35 U.S.C. § 102(b) as being anticipated by Wei et al., Peptides, 1998; 19: 1183-1190 ("Wei").

Wei discloses a study of the activities of corticotrophin-releasing hormone (CRH)-related peptides and several analogs in cells transfected with either CRH_1 or $CRH_{2\beta}$ receptors, in suppression of heat-induced rat paw edema in pentobarbital-anesthetised animals and in

stimulation of release of immunoreactive corticotrophin (ir-ACTH) from rat anterior pituitary tissue *in vitro*. In the cells transfected with CRH_1 receptors, the tested peptides, human/rat CRH, r-urocortin, h-urocortin, white sucker fish/maggy sole urotensin I and analogs of these peptides substituted with D-amino acids. Further, the article teaches that the actions of CRH are mediated by specific G-protein coupled receptors, wherein two major subclasses have been identified, CRH_1 and CRH_2. Wei does not describe synthetic CRH-R1 and/CRH-R2, but rather, describes cells transfected with CRH_1 or $CRH_{2\beta}$. Further, Wei does not describe pharmaceutical composition and/or kit wherein the one or more synthetic CRH-R1 antagonists and/or CRH-R2 agonists is directly modifying a response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis. Accordingly, claims 4-8 and 13 are not anticipated by Wei.

VII. Non-obviousness of the Present Invention in View of the Cited References

Additionally, Applicants respectfully submit that the present invention is patentable over the cited art. Even though the cited art is aimed at investigating, in different aspects, how the CRH receptors respond to different stimuli none of the references describe agonists/antagonists of the receptors as having the recited therapeutic modalities. There is no disclosure of compounds in the cited art having an agonizing/antagonizing effect on the CRH-receptors, as constituents in pharmaceutical compositions for treating inflammation at the level of macrophages in contrast to fighting (e.g., the aetiological cause of the macrophage activation). In particular, there is no disclosure of pharmaceutical compositions or kits comprising CRH agonists/antagonists that directly modify the response of monocyte/macrophage cell activation, proliferation, differentiation or apoptosis.

The effect of the direct modifying feature of the present invention is that a sustained modification of the macrophage machinery is obtained whereby inflammatory diseases are treated. Such effect is particularly illustrated by the results discussed in the specification on page 24-26, where UCN levels in different stages of inflammation are measured. This is completely distinguishable from what is reported by Webster, for example, because the present invention examines the direct effect of CRH-R1 and CRH-R2 receptor agonists and/or antagonists on monocyte/macrophage cells as a way to intervene in the treatment of inflammatory diseases.

Hence, the present inventors disclose products and methods specifically using CRH agonists and/or antagonists via the specific CRH-R1 and CRH-R2 receptors on monocytes and macrophages in intervening therapeutically in specific inflammatory diseases where monocytes/macrophages play a crucial role via specific signaling pathways. Consequently, the present inventors disclose a specific mechanism of therapeutic intervention and not general and non-specific effects of a single compound.

Neither Webster nor any of the other cited art references disclose, teach or suggest such mechanism. Thus, there is no obvious way to arrive at the present invention from any of the prior art documents alone or in combination.

Furthermore, the effect of a given putative pharmaceutical compound is not predictable and it is unobvious in view of the cited art that agonists/antagonist of the present invention have the claimed effect.

The fact that antalarmin inhibits/antagonizes hormone production from CRH activated macrophages does not imply that synthetic CRH-R1 antagonists and/or CRH-R2 agonists are potent compounds for direct modification of monocyte/macrophage cell activation, proliferation,

differentiation or apoptosis. Thus, it is well known in the art that synthetic antagonists/inhibitors are not necessarily suitable pharmaceuticals.

For the above reasons, it is respectfully submitted that the present invention is not disclosed, taught or suggested by the cited art, alone or in combination.

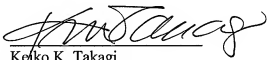
VIII. Conclusion

In view of the above, reconsideration and allowance of the claims is respectfully requested.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned attorney at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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